

# Tailored dosimetry in the radioiodine treatment of differentiated thyroid cancer

Citation for published version (APA):

Wierds, R. (2018). *Tailored dosimetry in the radioiodine treatment of differentiated thyroid cancer*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20180530rw>

## Document status and date:

Published: 01/01/2018

## DOI:

[10.26481/dis.20180530rw](https://doi.org/10.26481/dis.20180530rw)

## Document Version:

Publisher's PDF, also known as Version of record

## Please check the document version of this publication:

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# Valorisation



## Relevance for society

Thyroid cancer is the most frequent endocrine malignancy having a yearly incidence of 3.1 and 9.3 per 100,000 for men and females, respectively. The last decades, the yearly incidence of thyroid cancer has shown a significant increase worldwide. Differentiated thyroid cancer (DTC), in which specific iodine uptake is preserved, comprises the vast majority of all thyroid cancers. When adequate treatment, including radioiodine therapy, is given, the prognosis of DTC is in general excellent for patients showing no distant metastases.

In clinical practice, empirically determined fixed amounts of radioiodine are generally administered in radioiodine therapy in DTC, according to Dutch and international guidelines. In this approach, the amount of radioiodine to be administered is based on disease and patient characteristics. However, it has been shown that radioiodine uptake of iodine-avid lesions, and thus the lesion absorbed radiation dose, varies highly, not only between different patients but also between different lesions within the same patient. In addition, radioiodine treatment in DTC patients may result in adverse effects such as salivary gland dysfunction, transient gonadal dysfunction and secondary primary malignancies which have been shown to correlate with increasing radioiodine activity. As a consequence, the fixed activity radioiodine therapy approach may result in an under- or overdosing of patients. Indeed, for patients presenting with distant metastases, chances of successful therapy are decreased substantially. In addition, recurrence rate after initial treatment is relatively high and subsequent radioiodine therapy is needed in a considerable number of patients.

As an alternative to the fixed-activity approach, pre-therapeutic dosimetry assessment can be used to facilitate personalized radioiodine treatment. In fact, according to the 2013 council directive of the European Union, a tailored dosimetry approach is required for all medical radiotherapeutic purposes, including radionuclide therapy. In this thesis we have shown in a retrospective study that a personalized radioiodine approach, using pre-therapeutic  $^{124}\text{I}$  PET/CT based lesion dosimetry, provided prognostic information with respect to lesion response. Therefore, we conclude that a personalized dosimetry approach may be useful in DTC patient management, in particular for high-risk patients.

## Target groups

The results of our studies with respect to  $^{124}\text{I}$  PET based lesion dosimetry are of interest for radiologists and nuclear medicine physicians, endocrinologists, medical physicists, radiation protection experts and, most importantly, in the future also for patients suffering from DTC. The application of a tailored dosimetry approach in DTC may result in optimized and individualized radioiodine treatment. On the one hand, this would facili-

tate lesion dose escalation and may improve patient outcome, which is in particular important in high-risk DTC patients presenting with distant metastases. On the other hand, for patients with lesions showing high radioiodine uptake, a personalized treatment approach may yield lower amounts of radioiodine used in therapy and result in less adverse effects.

The results of our study to the contribution of ceiling scatter to the total radiation dose outside nuclear medicine treatment rooms are of interest for radiation protection officers, radiation protection experts and medical physicists and allow for improved shielding designs in nuclear medicine departments which are save, cost effective, and in line with the applicable legislation.

## Activities

The overall aim of this thesis was to improve radiation dose assessment in radioiodine treatment in DTC, both for the application of personalized patient treatment using quantitative  $^{124}\text{I}$  PET imaging and radiation protection of personnel and the general population. To this end, first we provided an overview of currently used personalized dosimetry approaches and relevant developments in the field of molecular nuclear therapy. Moreover, we investigated the quantitative characteristics of PET/MRI with respect to  $^{124}\text{I}$  PET lesion dosimetry in radioiodine therapy in DTC patients. Using both phantom and patient data, we showed that accurate  $^{124}\text{I}$  PET/MRI quantification with the aim of performing pre-therapeutic lesion dosimetry in DTC patients is feasible in a clinical setting. As PET/MRI offers a superior soft-tissue contrast in the head-neck region compared to PET/CT, in the future, PET/MRI may become increasingly important for specific clinical tasks (such as children with DTC) or, at least, in combination with PET/CT a modality of choice for  $^{124}\text{I}$  PET imaging in DTC patients. In addition, we investigated the impact of a novel sinogram-based prompt gamma coincidence correction technique on  $^{124}\text{I}$  PET uptake quantification and on the lesion absorbed dose estimation in DTC. It was shown that prompt gamma coincidence correction may have a substantial impact in a personalized radioiodine approach, in particular for small lesions showing low  $^{124}\text{I}$  uptake, and should be applied whenever available.

So far, the results described in this thesis have been reported in one review article and three original research articles that were published in peer-reviewed scientific journals in the field of nuclear medicine or medical physics. In addition, results were presented on the international congress of the European Association of Nuclear Medicine.

## Innovation

Although dosimetry in radionuclide therapy is still greatly in development, advanced tailored dosimetry based on pre-therapeutic imaging has been reported feasible in recent years. Important developments in nuclear medicine instrumentation improving (quantitative) image quality such as hybrid SPECT/CT, PET/CT and PET/MRI systems, time-of-flight PET, digital PET detectors and novel advanced reconstruction algorithms using sophisticated physics models have become commercially available. In addition, the development of dosimetric software programs capable of performing personalized dosimetry is still evolving at high pace.

Implementation of a pre-therapeutic  $^{124}\text{I}$  PET dosimetry approach in a clinical setting is limited as a result of a lack of supporting evidence from randomized controlled trials, long standing professional traditions, personal expertise and reimbursement issues. Furthermore, reliable lesion dosimetry is technically challenging, time consuming and expensive.

In this thesis we have shown in a retrospective study that lesions showing complete lesion response to radioiodine therapy received a statistically significant higher lesion absorbed dose, assessed from pre-therapeutic  $^{124}\text{I}$  PET/CT, compared to lesions showing no or incomplete lesion response. Moreover, pre-therapeutic  $^{124}\text{I}$  PET/CT based lesion dosimetry provided prognostic information with respect to lesion response to radioiodine treatment, indicating that a personalized dosimetry approach may be useful in patient management and improve treatment outcome.

## Planning and realisation

The research described in this thesis was performed in a close collaboration with the university hospital of Essen and the university hospital RWTH Aachen. In addition, for one study we collaborated with the university hospital of Essen, and the university of Twente.

Hybrid PET/MRI systems have recently become commercially available. Although to date no studies have been published in which the added value of  $^{124}\text{I}$  PET/MRI imaging in DTC patients was investigated for a large number of patients, this thesis demonstrated the feasibility of performing pre-therapeutic  $^{124}\text{I}$  PET/MRI based lesion dosimetry. As PET/MRI offers a superior soft-tissue contrast in the head-neck region compared to PET/CT, PET/MRI may provide important added value over PET/CT imaging and may become a modality of choice for  $^{124}\text{I}$  PET imaging in DTC patients in the future.

The concept of performing personalized radioiodine treatment in DTC patients, in which radiation absorbed dose calculations are considered in the decision-making of the amount therapeutic radioiodine to be administered in therapy, is described in the latest guidelines of both the American Thyroid Association and the European Associa-

tion of Nuclear Medicine. Moreover, the application of pre-therapeutic lesion absorbed dose assessment has been reported to result in a change in patient management for a substantial number of DTC patients. However, personalized radioiodine treatment based on pre-therapeutic dosimetry calculations is not recommended in the latest guidelines on radioiodine therapy in DTC as the biologic effectiveness of dosimetry-guided approaches has not been proven yet. In fact, to date, prospective randomized controlled studies addressing the optimal activity approach are lacking. Based on our results that showed that <sup>124</sup>I PET-based lesion dosimetry provides prognostic information on lesion response, we would strongly advocate cooperative efforts to establish a multicentre prospective <sup>124</sup>I trial to investigate the potential benefits of a personalized radioiodine approach over the empirically determined fixed-activity approach.